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Title

Challenges in the interpretation and therapeutic manipulation of human ingestive microstructure

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Abstract

This Mini-Review focuses on the interpretative value of ingestive microstructure by summarizing observations from both rodent and human studies. Preliminary data on the therapeutic manipulation of distinct microstructural components of eating are also outlined. In rodents, the interpretative framework of ingestive microstructure mainly concentrates on deprivation state, palatability, satiation and on the role of learning from previous experiences. In humans, however, the control of eating is further influenced by genetic, psychosocial, cultural, and environmental factors which add complexity and challenges to the interpretation of the microstructure of meal intake. Nevertheless, the presented findings stress the importance of microstructural analyses of ingestion, as a method to investigate specific behavioral variables that underlie the regulation of appetite control.

THERE IS A QUEST for decoding the effect of hunger, appetite, and satiety on specific quantitative components of meal intake (9, 16, 17). The ultimate goal is to understand the behavioral mechanisms that control pathologic eating patterns associated with obesity or anorexia. Microstructural analysis of intake is considered to be a precise and relatively inexpensive diagnostic modality to identify specific psychological and physiological parameters underlying the regulation of appetite control and has been primarily used in animal research (40). However, recent technologic improvements enabled the application of microstructural and meal pattern analyses also in humans (59, 79).

Over the last decades, high definition recording of nutrient intake within one single meal of solid or liquid food, or during breast-feeding, has been deployed in human research (12, 28, 45). More recently, data collection has been facilitated by a variety of wearable sensors, which detect meal patterns and food intake dynamics that occur under real-world circumstances (36). Device-assisted techniques may complement or even replace traditional methods of data collection, such as food diaries and food preference questionnaires (20, 51). Since the regulation of eating is under the control of more factors then just caloric need, the interpretation of the temporal organization of meal intake remains a complex challenge in the field of behavioral neuroscience (4, 23, 27).

Studies in rodents have demonstrated that microstructural parameters of meal intake, i.e. the size and number of ingestive bursts or lick rate, are under the control of opposing features. Pre-meal hunger and palatability of the nutrient have a stimulatory effect, while satiation, innate taste aversion and learning from previous unpleasant postingestive consequences halt nutrient intake (61). The length of pauses between licks can be used to identify bursts or clusters of licks. A shorter pause, an inter-lick interval, occurs between licks within a burst, for example when the animal accumulates nutrients in the oral cavity or swallows between licks. Longer pauses between a pair of licks, inter-burst intervals, reflect neural processes that integrate ingestive signals (61).

Although findings in diverse animal models are informative, one must “keep in mind that not everything we observe in mice or rats is fully applicable to man” (58). And perhaps not even to animals living in the wild, since controlled laboratory conditions may fail to account for the social influences on food preferences, as it has been demonstrated in Norway rats by *Galef* (25). From an evolutionary perspective, it has been suggested that humans decreased their bite size in response to our increasing capabilities of extra-oral food processing, e.g. by the use of stone tools and fire (75). Human eating habits show a large inter-individual variation (20) and are under the influence of countless motivational drivers (46, 78) with variable proportional influence on meal size between individuals and over time. However, extremes in eating style have shown associations with pathologic conditions. For example, *slowness in eating* is a characteristic of the picky eating profile, which may be the manifestation of eating-related psychosocial impairment and anxiety (21). *Fast eating* tends to be linked with more energy intake during an *ad libitum* meal and shows correlation with excess body weight and metabolic syndrome (6, 55). Consequently, cognitive interventions that promote the deautomatization of such eating habits have been developed to prevent overeating and the risk of obesity (71).

Human applications of microstructural analysis of meal intake have resulted in conflicting findings (27, 46), therefore the purpose of this Mini-Review is to provide an overview on parameters that influence ingestive microstructure and to highlight the most recent analytical and interventional developments in this field.

How to define a meal?

The total amount of food intake in a given time reflects the number of meals multiplied by average meal size. Both the number and the size of meals show large variations, and both frequent snacking and the consumption of large portions have been associated with the rising prevalence of obesity (49, 60, 67). Although most species organize their feeding behavior into meals, there is little consensus on the appropriate definition of a meal and this certainly adds some bias to the comparability of available studies (27). The variety of approaches to defining eating occasions has been summarized in previous reviews (46). In order to provide a meaningful criterion of a single meal by taking the decrease in satiety between meals and the increase in satiation during meals into account, *Tolkamp et. al.* introduced a data-driven methodology by fitting a mixed model of log-normals to the frequency distribution of between-feeding interval lengths (73). After fitting these models, the best meal criterion estimate is the interval length where the Gaussian models of between-meal and within-meal intervals are equal.

Although this approach is non-arbitrary, reproducible, and provides respective meal criteria for different species based on their own behavior, its widespread application is burdened by the need for abundant and reliable records of “feeding events” in order to "feed" the statistical model with sufficient data. In this respect, data from animals currently seem to be more readily available due to the recording apparatus that has been in use for decades, such as electronic feeders and food containers that monitor weight of their content at regular intervals (74). However, a Delphi panel of experts recently agreed on the great potential of big data in obesity and in human population research (76). The experts foresee an abundance of data describing human ingestive patterns in the near future, mainly due to the development and availability of wearable motion sensors and the capacity of mobile phones to record food intake (36). Meal size in humans is determined by innumerable factors related to the consumer, the food and the environment (Figure 1.). Therefore big data analytics, computational decision-making models (26) and correlation estimates of ingestive parameters with clinical and societal factors (70) may be extremely useful in revealing the role of different influencers on the organization of food intake (72, 89). However, one should keep in mind that "big data" is very heterogeneous and non-standardized, limiting its interpretative properties.

Attempts to decode the microstructure of meal intake

Available data on human ingestive microstructure are mainly correlational in nature, whereas studies in rodents mainly derive from hypothesis-based research paradigms using various recording techniques. The development of a universal eating monitor in 1980 was an important milestone in broadening the human diagnostic armamentarium (44). This machine is able to record food intake at 0.33 Hz by continuous weighing of the food reservoir by means of a concealed electronic balance and to compute total caloric intake, meal duration, initial rate and deceleration of food intake. More recently, *Kissileff et al.* validated a new sipometer in humans to measure the reward value of food and the motivation to consume (38). The idea was to translate a methodology developed in animals, by creating a system that enables the application of a progressive ratio licking paradigm, measures overall intake, meal duration, and the pressure exerted while sipping (43).

Table 1 summarizes the previously described associations between microstructural outputs and relevant physiologic or clinical parameters. Data from rodent and human studies are presented separately, allowing the comparison of interpretative approaches across species. Given the paucity of data and the heterogeneity in study designs, the main strength of the presented studies lies in their ability to show the direction of changes of microstructural parameters, as a function of physiologic state, palatability, satiation, stage of obesity or sex. The intake over time within a meal is often S-shaped, framed by a stimulation phase and a final satiation phase (72). The majority of human studies with direct measure of meal consumption focused therefore on eating speed and temporal changes in cumulative intake, often described as dynamic units of change in rate of consumption throughout the meal (30).

<u>*Initial ingestion rate*</u>

Rodent experiments, using different sucrose concentrations as stimuli, demonstrated that the initial rate of licking is increased in response to the gustatory stimulation produced by sucrose (80). It has also been shown, that deprivation increased the initial rate of licking at lower sucrose concentrations (18).

Similar observations have been made in humans in an *ad libitum buffet* setting where sandwich quarters were at disposal: initial ingestion rate (intake within the first 5 min) for lean and obese subjects was influenced both by palatability and deprivation state (66). Further, a chocolate pudding taste test using the universal eating monitor revealed that the initial eating rate in participants with overweight was higher than in normal weight controls (2.8 vs. 1.8 g/s) (45).

<u>*Lick/chew frequency within a burst*</u>

Rhythmic eating movements, such as licking or mastication, occur at a customized rate and reflect the output of a group of neurons functioning as a central pattern generator (61). In rodent experiments with manipulations related to deprivation state, palatability, or gastrointestinal re-arrangements (bariatric surgery), the inter-lick intervals remained quite stable (range= 150-170 ms) (48, 64). Nevertheless, intracerebroventricular administration of cocaine- and amphetamine-regulated transcript increased the average length of the inter-lick interval dose-dependently, and overall, produced a hypophagic effect (2). However, this could be due to a direct effect on the pattern generator rather than a specific satiation effect. Human studies also found a stable chewing/licking frequency across different conditions, including sex, bite size, different food, deprivation state or body weight (range= 1.1 – 1.4/s) (28, 65). Remarkably, psychosocial stress under laboratory conditions was able to increase chewing frequency in a study where participants were offered various solid foods and chewing behavior was recorded with a sound sensor system (33).

Deceleration of ingestive rate during meal

Both rodent and human studies suggest that deceleration of intake toward the end of a meal reflect the oral sensory control of the satiation process (8, 84). In a study involving women undergoing a warm test meal (rice, sliced chicken and vegetables), the cumulative intake curves could identify subgroups of decelerated and linear eaters. Linear eaters ate at an initially lower rate but were able to eat more food at a higher rate. In contrast, decelerated eaters had difficulty in further increasing their rate of eating. Linear eaters were less able to monitor their intake, therefore they seemed to be at risk of developing disordered eating (84).

Average eating rate

The interpretation of rodents' licking frequency changes as the meal proceeds (61). The initial rate of intake reflects the potency of gustatory stimulation, whereas the rate of intake later within the meal is influenced by conditioned and unconditioned negative-feedback related to orosensory and postingestive stimuli. Humans vary their rate of intake based on the nutrients' texture: solid food is often consumed at 10-100 g/min, whereas liquid beverages may be ingested at >600 g/min (52). It has also been observed, that overweight children eat more rapidly than their normal-weight counterparts (1). Further, genetic analyses involving twin participants objectified a heritability estimate of 0.62 for eating rate, which was at the top of the range of the heritability estimates among different appetitive traits (47). Slowing down the average eating rate appears to be an effective strategy for reducing food intake, and was even associated with greater ghrelin suppression in a recent study (32). Extremes in eating rate may reflect pathologic eating behaviors: anorectics consume small amounts slowly, whereas patients with bulimia/binge eating disorder tend to eat excessive amounts of food in a short period (6).

Lick/suck/bite/spoon size

In rodents, the influence of palatability of the stimulus on lick size has been demonstrated by the adulteration of water with quinine, which led to significant decrease in average volume per lick (64). Human studies showed that the control of bite size during eating is a highly dynamic process, affected in part by taste and olfactory sensations. When various concentrations of cream aroma were presented to the participants retronasally, higher aroma intensities resulted in significantly smaller bite sizes (87). Additional influencers are a brief visual pre-assessment of the portion size (larger portions tend to set off larger bites) (11), food texture (viscous, chewy and hard foods are ingested in smaller units) (88), and taste strength (smaller for a strong-tasting food) (7). Regarding the anthropometrics of the consumer, body mass index (0.20 g increase per point increase in BMI) (50) and male sex have been shown to be associated with increased bite size (57).

In the fields of pediatrics and neonatology, preliminary reports suggest a relationship between sucking patterns during breastfeeding (volume, strengths and duration of sucks) and later neurodevelopmental and motor outcome, with weaker and smaller suction reflecting worse prognosis (14). The other end of the spectrum, high-pressure sucking, labelled as vigorous feeding style, was associated with the risk of developing greater adiposity later in the childhood (1).

Number and size of bursts

Fundamental research using rodents revealed that the total number of bursts generated within a meal is increased by food deprivation and decreased by the potency of gastrointestinal postingestive inhibition (40, 62). In contrast, average burst size seems to be responsive to stimulus palatability, also called as orosensory stimulation (40, 62). More recently, the role of mouse genetics on burst characteristics was objectified in an experiment where licking microstructure was analyzed in three different strains of mice (41). To our knowledge, no published research has directly tested the interpretative significance of burst-related characteristics in human adults. In an exploratory study involving healthy lean participants, our research group identified an association of male sex with higher burst volume of liquid stimuli, while total number of bursts did not differ between males and females (28).

Inter-burst interval

In rodents, the length of inter-burst intervals seems to be sensitive to palatability, deprivation state and to the feedback effect of ingestion (15). A study in humans using edograms showed no effect of palatability on the length of intra-meal pauses (5). In a more recent experiment performed with wearable sensors in humans under real life circumstances and ad libitum food intake, duration of intra-meal pauses showed a high variation, depending on individual eating habits and surroundings (20).

Therapeutic manipulation of human ingestive microstructure

Lifestyle interventions designed to modify eating behaviors and physical activity are the first option for weight management, since they are relatively inexpensive and have negligible risk of complications (10, 37). A recent meta-analysis showed that eating quickly was associated with increased BMI and obesity, emphasizing the importance of eating style, in addition to what and how much to eat (55). Behavior therapists argue that eating slowly enables an individual to savor the taste of the food and to appreciate the sensory experience of eating which consequently enhances satiation (65). Various novel methods of therapeutic manipulation of distinct components of ingestive microstructure are presented in Table 2.

Eating rate

Slowing down eating rate seems to maximize the effectiveness of physiological satiation cues, however, this requires repetitive training to develop (22). To better assist patients in this process, several novel feedback systems have been recently developed.

The Mandometer™ consist of a wireless electronic scale that feeds real-time information on the decrease of the weight of the plate into a smart-phone application, which can be used in both clinical settings and in the everyday life environment (56). The subject can adapt his or her ingestive rate to a reference curve, which appear superposed to each other on the screen of the phone during meal intake. To validate the concept in children with obesity, a randomized controlled trial has been performed, where participants were randomized in two groups receiving dietary and activity advice either with or without additional Mandometer™ training (31). The trial failed to meet its objectives in terms of recruitment, treatment adherence, attendance at follow-up appointments, and ultimately failed to demonstrate a reduction in speed of eating in sufficient numbers of children.

It is more acceptable to most users when the sensing technology is embedded into a conventionally-used item, like eating utensils. As an example, the Sensing Fork™ can detect its user's eating actions and was found to be helpful in decreasing children's picky eating behavior when connected to a playful smart-phone application (42). In adults, vibrotactile feedback delivered through an augmented fork was found to reduce eating rate (35).

Bite size

In complement to interventions aiming to reduce eating rate, the reduction of bite size may reduce the risk of overconsumption (3). The effect of food diameter on bite size per mouthful has been investigated in laboratory conditions using a masticatory counter, which recorded number of chews simultaneously with electromyographic activity in the masseter muscle (60). Findings suggested that the mere decrease of food diameter / portion size might be a conveniently modifiable factor to decrease bite size and thus to control food intake.

Bite number

The term "mindless margin" has been introduced to describe the trend when people overeat without noticing it (78). It has been shown that environmental cues (i.e.: parallel activity, portion size, plate size, social interactions, etc.) can enhance meal size within the "mindless" framework. To counterbalance these unconscious orexigenic effects, objective intake monitoring technology has been introduced to help individuals keeping track of their consumption (39). Preliminary experiences with the Bite Counter™, which is worn on the wrist and uses a gyroscope to track wrist motion, found a reduction in overall consumption of a single meal in response to continuous feedback on the number of bites taken, without affecting the enjoyment of the eating experience (39, 79).

Burst volume

Given the methodologic and conceptual challenges related to the definition and assessment of burst size during everyday meals, this parameter of ingestive microstructure remained so far below the radar of behavioral interventions. However, interventions aiming to keep burst volume in a "healthy" range, which remains to be defined in large scale observational studies, may have a meaningful contribution in the treatment of obesity. To fill this data gap, our group recently performed a pilot study to analyze the ingestive behavior following Roux-en-Y gastric bypass (RYGB) in humans using a custom-built and validated drinkometer (28). Preliminary data suggest that the postbariatric reduction in overall food intake in humans is due to smaller burst sizes and not to decreased number of bursts (29) which is in accordance with previous animal data (48). In rodents the early postoperative licking profiles indicative of the motivational potency of the stimuli remained unchanged. In humans however, the highest decrease in burst volume (~75% from baseline) was measured in the early postoperative period and a steady increase from this nadir to 50% of preoperative values was observed by the end of the first postoperative year. This ingestive pattern preceded weight-loss, it manifested in all patients (*unpublished data*), and may be explained in part by an effect of RYGB in increasing the postingestive caloric sensibility (40, 54). Although these observations need to be confirmed in future studies using solid food stimuli and larger cohorts, they already provide an ingestive phenotype (68), which may be used as a reference when cognitive interventions targeting obesity are designed.

Inter-burst interval

There is a paucity of data on intentional interruptions of meal intake. *Yeomans et al.* were surprised to find an increase in food intake when the experimenters artificially divided a pasta meal into a series of short bouts (82). The relatively lower consumption under uninterrupted conditions were explained in part by habituation to eating due to monotony, and by the earlier development of sensory specific satiety.

Outlook

The present article aims to present available physiologic and clinical data on the microstructure of ingestion in humans and to offer perspectives for applied implications. Results showed the complexity and challenges in the confident interpretation of human-derived data. The interpretative framework which was carefully constructed in laboratory rodents, where different microstructural parameters were shown to be the function of deprivation state, palatability, satiation and learning from previous experiences, seems to be bewildered in humans by a myriad of genetic, psychosocial, cultural, environmental factors and by personal and situational norms (34). Nevertheless, the presented findings stress the importance of microstructural analysis of ingestion in humans as a promising method to investigate specific behavioral variables that underlie the dysregulation of appetite control. Preliminary results of behavioral manipulation of microstructure are promising and their implementation is supported by novel wearable technologies. These wireless devices and large public databases may add significant information in future studies aiming to assess the influencers of ingestive behavior under real life circumstances, allowing the consideration of multiple contextual factors inherent to eating.

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AUTHOR NOTES

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TABLES

Table 1. Associations of microstructural parameters of meal intake with properties of the stimulus or with physiologic parameters

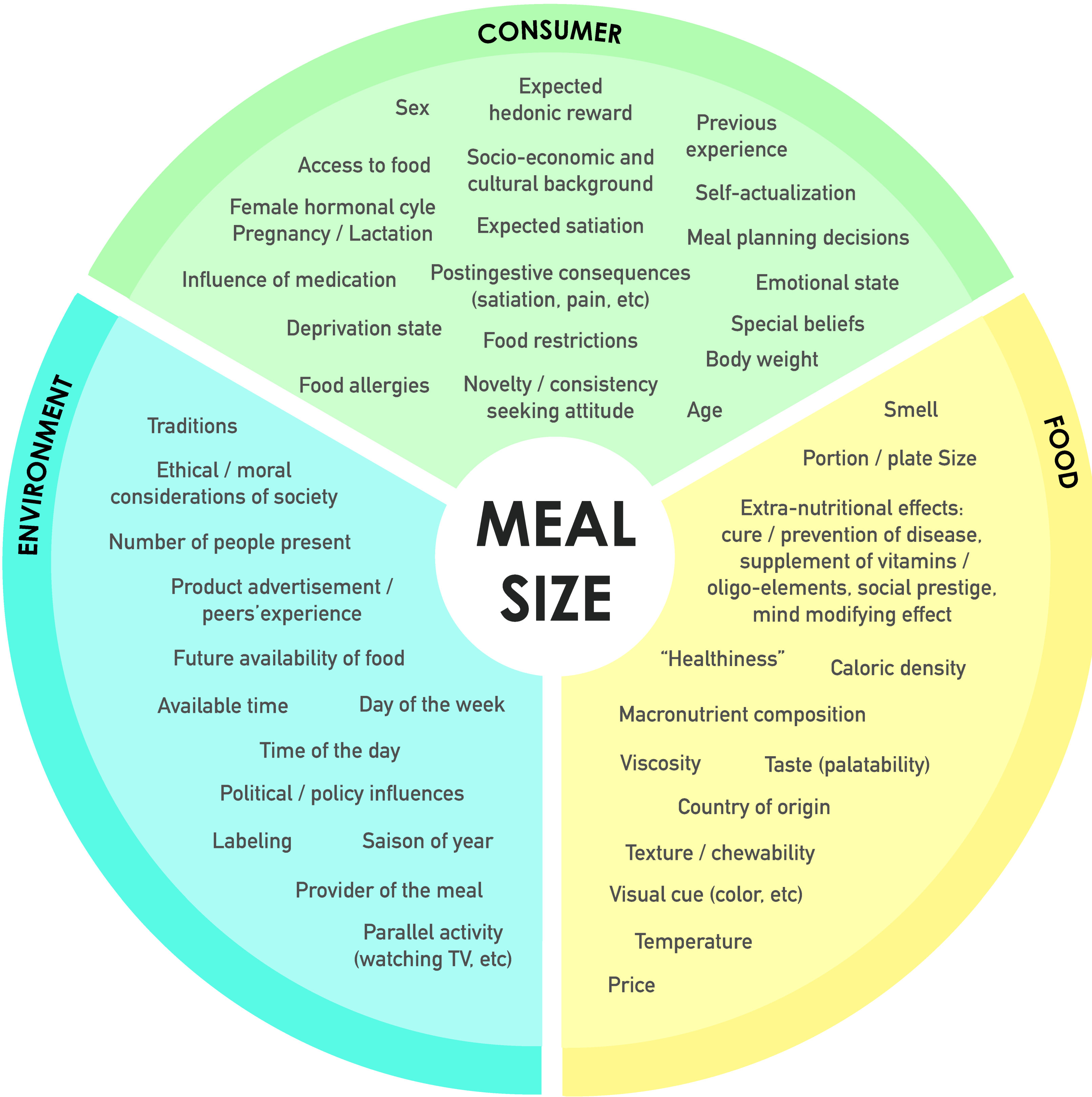
Microstructural parameter	In rodents	In humans
Initial ingestion rate	↑palatability (61); ↑deprivation state (18, 63); ↓anhedonia (13)	↑palatability (more in obese) (65); ↑deprivation state (65); ↑overweight (45); ↑male sex (65)
Lick/chew frequency within a burst	↔stable across conditions (lick/sec) (output of central pattern generator) (13, 61) ↓ anorexigenic substances (2)	↔ stable across gender and bodyweight-groups (~1.2 chew/sec) (65); ↑psychological stress (~1.6 chew/sec) (33) ↓ fullness and satiety (24)
Deceleration of ingestive rate during meal	↑satiation (8)	↑postingestive inhibition (84)
Average eating rate	↑reduced negative feedback (40, 61)	↑palatability (81); ↓anorexia nervosa and ↑bulimia (6), ↑excess body weight (55), ↓reduced enjoyment (32) ↔ role of heritability is high (47)
Lick/suck/bite/spoon size	↑palatability (64)	Adults: ↑obesity (~ +0.20 g/BMI point) and male sex (50, 65); ↑softer foods (52); ↓strong-tasting food (52) Neonates: ↑healthy neurodevelopment (14, 53)
Number of bursts	↑deprivation state (62, 69), ↓satiation/post-ingestive consequences (41), ↓conditioned and unconditioned negative feedback (40, 61), ↓reward devaluation / behavioral activation (13)	No available information was found
Average burst size	depends on orosensory feedback (40, 61); ↓satiation (41)	Adults: ↑male sex (28) Neonates: ↑healthy neurodevelopment (14, 53)
Inter-burst interval	Under unidentified probabilistic control of the central nervous system (15) Unaffected by sucrose concentration (19)	Depends on individual eating habits or environmental factors (20) Uninfluenced by palatability (5)

Table 2. Initial experiences with intentional modulation of human ingestive microtructure

Targeted microstructural parameter	Technique	Preliminary outcomes	Remarks
Eating rate	Pneumatic interface for shape-changes of eating utensils (86)	Has not been tested clinically	The utensil intervenes with food intake by bending/deflating upon detection of eating behavior using a motion sensor
	Mandometer™ (Mandometer, Brighton, Victoria, AU) is a portable scale connected to a computer that generates a real-time graph of weight representing food removal from a plate (56)	A pilot study showed reduced excess food intake in children (85), however a randomized controlled study failed to replicate results due to failure of families' engagement with primary care weight management interventions (31)	Algorithm automatically extracts cumulative food intake curves. User friendly interface with a mobile phone application, which shows the cumulative intake curve in real-time superposed to a reference curve.
	Smart fork (42)	Potential improvement in children's eating behavior (picky/distracted eating)	Playful device which provided users with visual feedback according to the eating behavior detected by the fork
	Intraoral device consisting of two thermoplastic splints (77)	The change of eating behaviour translated into sustained weight loss during long-term follow-up (15–38 months), where the patients (n = 6) continuously lost weight without using the device	Designed to slow the eating process, with the intent of prolonging the chewing process and delaying the swallowing of a single bite in order to improve the function of physiological satiation mechanisms.
Bite size	Decreasing food diameter might be a conveniently modifiable factor to decrease bite size (60)	Average bite size increased by 0.22 g for every 100 g increase in portion size (3)	Increase in portion sizes grew in parallel with increasing body weight in US (83)
Bite number	Bite Counter™ (39)	Feedback on the number of bites taken from a wearable intake monitor can reduce overall intake during a single meal	The Bite Counter™ is worn like a watch and tracks wrist motion to detect a pattern indicative of a hand-to-mouth gesture.
Burst volume	Roux-en-Y gastric bypass (29) (unpublished data from a prospective clinical study, ClinicalTrials.gov Identifier: NCT03747445)	Average burst volume of liquid meal intake decreased immediately after the operation, and at 1-year the mean decrease was 55% from preoperative values	This observation may be explained by pleiotropic changes in postbariatric physiology: increased intestinal caloric rate; increased gut hormone response; changes in vagal nerve signaling, in bile acids and in gut microbiota
Inter-burst interval	Food intake monitor with introduction of pauses after every 50 g consumed (82)	Introduction of timed pauses within meals significantly enhanced overall intake	Seems counterintuitive, since lower eating rate is known to decrease meal size. Pausing could alter the rate at which sensory specific satiety develops and disrupt monotony of eating.

FIGURES

Figure 1. Potential influencers of meal size in humans, grouped into three main categories.


CONSUMER
Sex
Expected hedonic reward
Previous experience
Access to food
Socio-economic and cultural background
Self-actualization
Female hormonal cyle
Pregnancy / Lactation
Expected satiation
Meal planning decisions
Influence of medication
Postingestive consequences (satiation, pain, etc)
Emotional state
Deprivation state
Food restrictions
Special beliefs
Body weight
Food allergies
Novelty / consistency seeking attitude
Age
ENVIRONMENT
Traditions
Ethical / moral considerations of society
Number of people present
Product advertisement / peers'experience
Future availability of food
Available time
Day of the week
Time of the day
Political / policy influences
Labeling
Saison of year
Provider of the meal
Parallel activity (watching TV, etc)
MEAL SIZE
FOOD
Smell
Portion / plate Size
Extra-nutritional effects: cure / prevention of disease, supplement of vitamins / oligo-elements, social prestige, mind modifying effect
"Healthiness"
Caloric density
Macronutrient composition
Viscosity
Taste (palatability)
Country of origin
Texture / chewability
Visual cue (color, etc)
Temperature
Price

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